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Abstract

At the interface of the plant systems biology and crop modelling communities, a recurring theme is the construction of an *in silico* plant that links across many levels of biological organisation. These disciplines are not mutually exclusive; each has some elements of the other and they have an overlapping goal in understanding and assisting crop improvement. Therefore, we believe that synergies can be gained through knowledge exchange between the two. Several modelling frameworks could support this aspiration. Our recent work on a multiscale Arabidopsis Framework Model (FM) combined concepts from both systems biology and crop modelling. We use the FM as a starting point to explore the potential benefits and challenges of applying and extending such cross-disciplinary tools.

Keywords: systems biology; crop modelling; *in silico* plant; multiscale; climate change; breeding

1.0 Introduction

The uncertain impact of climate change on crop yield has prompted various efforts to improve the predictive performance of crop models. Recent efforts included systematic comparisons of existing models and quantifying the uncertainty associated with each model, which has brought to fore the variety of model structures, assumptions and the approaches used in developing the models (Asseng et al., 2013; Rosenzweig et al., 2014). Studies have also extended beyond functional-structural plant models (FSPM) and process-based models (PBM), to consider organ level and genetic information that inform yield at the crop level (Chenu et al., 2009; Reymond et al., 2004).

The incorporation of genetic information that governs plant traits is not new. Gene actions were represented in earlier studies through linear estimates of effects on parameters to model different cultivars (Hoogenboom et al., 1997; White and Hoogenboom, 1996). More recent work linked crop models to quantitative trait loci (QTL), thus refining the representation to associated genomic regions (Reymond et al., 2003; Yin et al., 2005), though they are restricted to environmentally stable QTL (Chenu et al., 2009). Further refinement to molecular or gene network models has also been proposed (Hammer et al., 2006). The explosion of understanding in plant gene networks offers an opportunity to link the physiology of the plant and crop to mechanisms at the molecular level, and potentially thereafter to genome sequences.

Besides improving agricultural management, crop models have been useful in aiding crop breeding efforts (Chapman, 2008). Models can be used as preliminary screening tools to predict the performance of crossing existing cultivars before further tests are conducted, thus reducing the time taken to produce new cultivars. Recently, synthetic biology has been proposed as another alternative to conventional breeding, whereby varieties with desired traits are designed by modifying specific gene(s) through genetic engineering (Baltes and Voytas, 2015).

Evaluating alternative engineering strategies will often require quantitative models with explicit representation of the target gene networks, linked to their physiological functions. Moreover, the growth of genome sequences is expected in future to allow the mechanistic understanding of (some fraction of) the causal sequence variation between crop varieties. Again, linking the genomic data to quantitative mechanisms will require models that explicitly represent the functions of the relevant sequences.

Many physiological and genetic models have been developed for crops (Bogard et al., 2014; Gu et al., 2012), including a genetic network controlling wheat anthesis (Brown et al., 2013). However, quantitative models with gene networks, regulatory mechanisms and metabolisms are less common than in the model organism *Arabidopsis thaliana* (Lucas et al., 2011). One of the reasons is that crop models generally aim towards parsimony, i.e. capturing only the essential elements of environmental effects on plant performance. The availability of data was also uneven, as genetic tools to decipher molecular mechanisms have been relatively fewer in crop species; crop genomes are larger and more complex; and the timescales and/or facilities required for crop studies can be substantially greater. The majority of the plant gene functions discovered in the last decade have therefore been in Arabidopsis, making this the easiest species for mechanistic modelling, despite the considerable distance from crop models.

Emblematic examples of crop homologues for these Arabidopsis genes were quickly shown to underlie the high yield of crop varieties identified during the first Green Revolution (Ait-ali et al., 2003; Hedden and Kamiya, 1997; Peng et al., 1999; Sasaki et al., 2002). In recent years, many homologues of Arabidopsis genes have been found in crops (Chew and Halliday, 2011; Nakamichi, 2014). We are also seeing progressively more application of molecular and systems biology tools in crop studies (Kikuchi et al., 2003; Libault et al., 2010; Schmutz et al., 2010; Schnable et al., 2009). Different approaches have been suggested to make the best use of molecular plant science, systems biology and crop systems modelling in addressing the energy

crisis and food security issues (Hammer et al., 2004; Minorsky, 2003; Weckwerth, 2011; Yin and Struik, 2010). A recurring theme is to develop *in silico* or digital plants (Zhu et al., 2015), with integrative representation of gene functions at the molecular level while also linking across all biological levels of organisation, combining existing methods from crop dynamic modelling and the fast-emerging techniques in plant systems biology (Fig. 1).

This approach recognises the major opportunity for many more findings of basic plant research to support tangible crop improvement programmes. The considerable, financial and organisational constraints on the process have been reviewed elsewhere (RS, 2009). In this paper, we discuss whether and how multiscale models could provide a new technical avenue for research translation, with benefits for both fundamental and applied research. We propose the bridging of plant systems biology and crop systems modelling at various levels, where the different communities could complement one another (Fig. 1). As a case study, we discuss our recently published multiscale model of Arabidopsis growth (Chew et al., 2014) in relation to crop modelling, and where it stands relative to the *in silico* plant aspiration described above. We also present an example of the circadian clock gene network and its role in photoperiodism, because the molecular mechanisms are relatively well-understood, control important traits and have thus been studied in crops. Our aim here is not to propose this as the network of choice for genetic engineering, but to illustrate how systems biology models with molecular mechanisms may contribute towards crop designs for future breeding, including through synthetic biology. Similar principles could potentially be applied to many molecular processes that control crop traits.

2.0 The multiscale Arabidopsis Framework Model

104 The Arabidopsis Framework Model (FM) was developed using a modular approach by
105 combining published models without modifying them. The FM consists of component models
106 or modules that are characteristic of different research domains, such as molecular systems
107 biology (gene regulatory network), crop science (functional-structural and source-sink
108 relations at the organ level; phenology) and physiology (leaf-level photosynthesis; respiration,
109 metabolism) (Fig. 1). Below, we briefly review each module, its links with crop science and
110 translational potential.

111 **2.1 The biological clock and photoperiodic response mechanisms**

112 The module at the molecular level describes the gene circuit network of the circadian clock in
113 Arabidopsis, which is one of the pervasive molecular networks regulating photosynthesis,
114 metabolism and flowering time (Hotta et al., 2007). The circadian clock enables plants to
115 perceive the duration of sunlight (photoperiod), an important cue for seasonal timing, so that
116 plants can pace their daily biochemical reactions and developmental events to optimise growth
117 and escape unfavourable environmental conditions (Millar, 2016; Simpson and Dean, 2002).
118 The effects of photoperiod on developmental rates have been included in many crop models,
119 even though no molecular basis was discovered until more recently (Nakamichi, 2014; Turner
120 et al., 2005; Yano et al., 2000). Developmental transitions were related to seasonal changes,
121 using a photoperiod-dependent scaling factor to modify the cumulative thermal time required
122 for a developmental switch, measured in the photothermal units of phenology models
123 (Robertson, 1968). For some crop species, photoperiod appears to be an obligatory signal; this
124 is modelled using conditional functions where critical photoperiods must be exceeded before
125 the model can proceed with successive events (Dingkuhn et al., 2008). In the case of the FM
126 (Chew et al., 2014), the photoperiod-dependent scaling factor in the phenology module is a
127 function of the expression level of a flowering gene (*FLOWERING LOCUS T*, *FT*). *FT*
128 expression is linked to the clock gene circuit module, based on the well-characterised

129 photoperiod response network in Arabidopsis (Salazar et al., 2009). Here, gene expression is
130 modelled using a set of ordinary differential equations (ODEs), where the change over time of
131 each molecular component is simulated, along with their multiple responses to the light:dark
132 cycle. This formulation not only provides a direct linkage between individual genes in the
133 clock-photoperiodism pathways, environmental inputs and phenology, but also offers temporal
134 resolution within the day, i.e. the scaling factor for photoperiodic response is continuously
135 tuned to the dynamics of the flowering gene expression (Box 1). One advantage of this is that
136 the changing photoperiod sensitivity within a day-night cycle can be captured, for example to
137 compare the effects of different mutations for plants growing at different latitudes (Box 1).
138 This capability may facilitate the understanding of Genotype x Environment interaction,
139 specifically for crop varieties with genetic variation in the clock/photoperiodism genes (see
140 Section 3.0) (Nakamichi, 2014).

141 **2.2 Carbon metabolism**

142 Metabolism is modelled in the FM in a simplified manner; only sugar (the transported carbon
143 form) and starch (stored carbon) are considered (Gerakis et al., 2006). Sugar is transported
144 from source organs to sink organs for growth and respiration, while part of the assimilated
145 carbon is stored as starch during the day so that it can be converted into sugar at night when
146 there is no photosynthesis. A recent study in Arabidopsis has revealed a circadian-clock control
147 of starch consumption rate, which is paced so that there is enough starch to last the length of
148 the night (Graf et al., 2010). This is currently represented in the FM using a simple division of
149 total starch turnover by night period (Chew et al., 2014). More detailed models linking starch
150 degradation to the clock gene network are also available (Pokhilko et al., 2014; Seaton et al.,
151 2014). These models focus on a subset of the complex metabolic network: their scope could
152 readily be broadened. In recent years, genome-scale metabolic models have been developed
153 for several species, where the fluxes of all metabolites in a plant system are solved by

optimising within a set of constraints an objective function, e.g. maximising biomass or minimising total energy costs (Cheung et al., 2014; Grafahrend-Belau et al., 2013; Poolman et al., 2009). Such flux-balance modelling has been useful in identifying redundant or alternative pathways and their relative efficiencies, and can predict the shift in fluxes under different environmental conditions (Cheung et al., 2013; Williams et al., 2010), potentially with tissue resolution (Rolletschek et al., 2015). This level of detail is understandably not included in any crop models, nor is it usually considered in conventional breeding. Nevertheless, metabolic modelling can help identify target enzymes for breeding or genetic manipulation, to achieve desired metabolic outputs thus facilitating metabolic engineering (Schwender, 2008). A major limitation compared to single-cell organisms is that plant systems span a wide range of spatio-temporal scales. Changing a target enzyme may not be sufficient to translate metabolic gains into commensurate benefits at the whole-organism level (Leakey et al., 2012). The second opportunity for modelling is therefore to optimise the effect of modification at the genetic level on events at the whole-plant level and beyond. In this respect, models like the FM can provide a framework for linking metabolic models of increasing breadth to processes at the higher levels, to aid molecular breeding or synthetic biology.

2.3 Plant architecture

The FM also considers plant architecture, specifically shoot structure and its function in light interception for carbon acquisition. This is modelled using a functional-structural module where individual organ growth and leaf orientation are captured. The significance of plant architecture in crop yield has been explored; one good example is the extension of a 3D canopy model of wheat development to include mechanistic details such as organ-level photosynthesis and allocation of assimilate (Evers et al., 2010). Simulating canopy structure is useful in understanding competition for light, both inter-species and intra-species. Thus, crop models that consider plant form and function can be valuable for maximising crop yield per unit area

to optimise land use (Egli, 1988; Mao et al., 2014). In the case of Arabidopsis, this plant species has a simple rosette structure during the vegetative phase but upon switching to the reproductive phase, stem elongation and branching occur, forming a more complex inflorescence. The current version of the FM only models the simplest, vegetative phase. Including the developmental phases important for crops will allow future versions of the model to address the resource partitioning issues that are particularly relevant for translational research. An extension to include the functional-structural contribution of the inflorescence until fruit (and thus seed) formation is necessary (Christophe et al., 2008). These models would require comprehensive phenotypic and physiological data, some of which are available (Alonso-Blanco et al., 1999; Bennett et al., 2012; Diggle, 1997). Although the area seems under-explored in Arabidopsis relative to crop species, these studies have already revealed interesting correlations between branching and seed yield, which also depend on the plant varieties, and identified some related QTL regions. Indeed, a recent mechanistic model of sucrose transport in rice also highlighted the effect of grain arrangement on yield (Seki et al., 2015), suggesting that the genetic tools to manipulate carbon partitioning in Arabidopsis will allow future models to contribute further quantitative understanding of this area.

In contrast, plant development at the cellular, tissue and organ levels has been intensively studied in Arabidopsis. Many of the molecular mechanisms regulating cell geometry, tissue patterning and organ morphology have been elucidated using mathematical modelling (Roeder et al., 2010; Sauret-Gueto et al., 2013; Torii, 2012), which therefore provide opportunities for linking with the FM. As the FM already has a simple representation at the organ level, incorporating more detailed morphology will be a natural extension. Including geometry at the cellular level will require a major change in the resolution and hence in the modelling methods. Nevertheless, such extensions could provide a platform to further improve yield through altered

203 architecture, as a continuation of what has been achieved during the first Green Revolution
204 (Khush, 2001).

205 **2.4 Phenology**

206 Vegetative development is simulated in the FM by a phenology module (Chew et al., 2012;
207 Wilczek et al., 2009). This module utilises the thermal time concept, which is adapted from
208 crop modelling approaches. Three components contribute: thermal time, photoperiod (see
209 above) and vernalisation. Degree-days are integrated, scaled by the photoperiod and
210 vernalisation factors, until a threshold value is exceeded to indicate the switch from the
211 vegetative to the reproductive phase. Additionally, the FM also simulates the change in
212 phyllochron, which is another phenological event within the vegetative phase, driven by
213 thermal time. To model the whole life cycle, this module will need to include floral initiation,
214 fruit formation, seed development and maturity, and plant senescence after which seeds can be
215 harvested. Seed dormancy has recently been addressed (Springthorpe and Penfield, 2015).

216 Crop modelling techniques that already consider various developmental stages again offer
217 valuable examples. It is worth noting here that ontogeny is actually a continuous process. The
218 'discrete ontogeny' of functional stages allows plant development to be mathematically
219 represented as a sequence of states of finite automata (Komarov et al., 2003). Molecular events
220 that govern plant ontogeny are also continuous, and are often modelled as such in systems
221 biology, though hybrid discrete-continuous models have also been adopted such as for systems
222 exhibiting multiscale dynamics (Lincoln and Tiwari, 2004). Indeed, this is the approach used
223 in the FM, where the continuous gene regulatory module (see above and Box 1) was linked to
224 the phenology module. We expect more such hybrid links in the future, especially when
225 combining crop modelling concepts with those in systems biology.

The diverse technical approaches, which are natural in models from different research domains, can form a significant barrier to re-using large models. Model exchange standards such as SBML and CellML greatly facilitated progress in some areas of computational systems biology, through model sharing and dissemination (Chew et al., 2014; Le Novere, 2006; Le Novere, 2015). Further tools are required to increase computational efficiency and facilitate model analysis (Qiu et al., 2014), in addition to sharing experimental data (Leonelli et al., 2013). Furthermore, there are also platforms specific for the plant and agricultural research community (reviewed in Adam et al., 2012) like OpenAlea, APSIM and RECORD that support model composition (Bergez et al., 2013; Brown et al., 2014; Pradal et al., 2008). The FM used one such tool, Simile (Muetzelfeldt and Massheder, 2003), to refactor all four modules into a common format. These tools could mean that crop models and contemporary systems biology models can be more conveniently exchanged, reused and combined.

2.5 Photosynthetic engineering

One of the processes central to plant yield is photosynthesis. Crop models like APSIM, Sirius or CERES can effectively simulate growth based on organ demand or plant water status (Hammer et al., 2010; Hoogenboom et al., 1994; Jamieson et al., 1998). In these models, carbon assimilation (or dry mass accumulation) is explicitly modelled but crop growth is driven by phenological development and organ expansion. These approaches also offer the potential to link with systems biology, for as plant water relations (reviewed in (Tardieu et al., 2015); (Parent and Tardieu, 2014)) involve the intensively-studied guard cell signalling network, which was recently modelled in detail (Chen et al., 2012). The FM centres on carbon balancing with a photosynthetis representation using the classical Farquhar model (Farquhar et al., 1980) to simulate photosynthesis. The Farquhar model is commonly used in ecosystem models of carbon cycling, though it has also been adopted in some crop models (e.g. GECROS (Yin and van Laar, 2005)). This model and its later developments consider rate-limiting reactions like

carboxylation, electron transport and inorganic phosphate (Pi), using kinetic parameters measured at the leaf level (Farquhar and von Caemmerer, 1982; Sharkey, 1985). More recently, new tools in molecular, physiology, biochemistry and systems biology have facilitated the development of a more detailed model, e-Photosynthesis (Zhu et al., 2013), which has explicit description of individual reactions and major regulatory processes at the molecular level in the photosynthesis network. Models with such details have identified molecular components/pathways for improving photosynthetic capacity, which could serve as a blueprint for the bioengineering of crop species (Wang et al., 2014). The FM's modular approach provides an ideal platform to evaluate alternative modules, such as the coarse-grained Farquhar and fine-grained e-Photosynthesis models. A fine-grained model can explicitly represent the target enzymes and processes for engineering at the molecular level, providing the bridging platform to understand and optimise how candidate manipulations propagate into changes at the whole-plant level.

3.0 Classical breeding and directed design

The crops that we consume today have gone through centuries of human cultivation, during which one of the selection aims was to expand the regions where the plants can be grown and produce high yields. The mutations that were selected in the photoperiod pathways include variants in the crop homologues of several Arabidopsis circadian clock genes (see (Nakamichi, 2014) for a comprehensive review). Understanding in Arabidopsis has become the reference point for determining the functions of such mutated genes in crop cultivars (Box 1), such that the function of a growing number of genome sequence variants might in future be explained by reference to this system. A multiscale model such as the FM could extend the scope of such understanding, even if the other physiological processes reviewed above remain simply

represented in the model. The potential for synergy will grow as further modules gain mechanistic detail, such as the circadian regulation of starch metabolism noted above, especially if mechanisms identified and modelled in model species translate readily to crops.

As the demand for food and biofuel increases, the pressure of climate change could also restrict the temporal window for flowering (or other developmental events). A model-assisted breeding strategy, where crop cultivars optimised for specific regions are specially designed and bred or engineered, may open new avenues for local adaptation (Fernandez-Cornejo and Caswell, 2006). The mechanistic, molecular models would be a relatively small part of this process. Accurate climate models will be required to provide projected climate inputs (Gleckler et al., 2008; Knutti et al., 2010), though this is also an active research area (Duben et al., 2014; Refsgaard et al., 2014) Latitude-specific 'maturity groups' are well established in some crops, such as soybean (Boerma and Specht, 2004), but for other crops this would represent a major change in commercialisation. The *in silico* plant must therefore be considered within a broad research and translation agenda.

4.0 Concluding remarks

Our initial work on the Arabidopsis Framework Model is unusual in representing both plant systems biology and elements drawn from crop systems modelling. The FM might be seen as a 'boundary object' in sociological terms, at the interface of several research communities, potentially facilitating communication (Star and Griesemer, 1989). While the FM will clearly benefit from extension, it offers a medium to integrate the different types of understanding from fundamental plant research and crop models. Tools of this type also have significant potential to contribute to practical crop improvement, as one of several promising alternatives

298 that might be linked by umbrella structures such as the Joint Programming Initiative on
299 Agriculture, Food Security and Climate Change (FACCE-JPI).

300

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304

305 **Figure 1: *In silico* plant linking across biological levels of organisation**. Plants are complex
306 systems that cross multiple, interactive levels of organisation (column A). Each discipline (C)
307 usually focuses on processes at specific level(s) (B). Shaded boxes indicate processes currently
308 considered in our multiscale Arabidopsis Framework Model (Chew et al., 2014). Different
309 modelling communities (D) could interact and work together at various levels, where synergy
310 might be gained.

311

312 **Box 1. Connecting molecular circuits to flowering phenotypes.** The regulatory mechanisms
313 underlying the sensitivity of flowering time to photoperiod have been characterised at a
314 molecular level. This is illustrated in (A), showing a simplified representation of the regulatory
315 interactions involved in the circadian clock (orange) and the photoperiod pathway (green),
316 culminating in the regulation of *FT*. The dynamics of these networks have previously been
317 described by mathematical models (Pokhilko et al., 2012; Salazar et al., 2009; Song et al.,
318 2012), and were recently combined and updated in a single model (Seaton et al., 2015). This
319 allows simulation of the behaviour of this network in different natural photoperiods at different
320 times of year, for example those occurring in Halle, Germany (B). At different times of year,

the model simulates different levels of *FT* at this location (C). Thus, given a date of seedling emergence, the date of flowering can be predicted (D). Flowering times for different genotypes can also be predicted, e.g. in the case of the mutants *prr9;prr7* and *elf3* (knock-out mutants of circadian clock genes with orthologues in crop species (Staiger et al., 2013)). This allows simulation of a population of plants that show a distribution of dates of emergence. As shown in (E), the sensitivity of the wild-type plants to photoperiod means that flowering occurs over a narrower distribution of dates than either the late-flowering (*prr9;prr7*) or early-flowering (*elf3*) circadian clock mutants.

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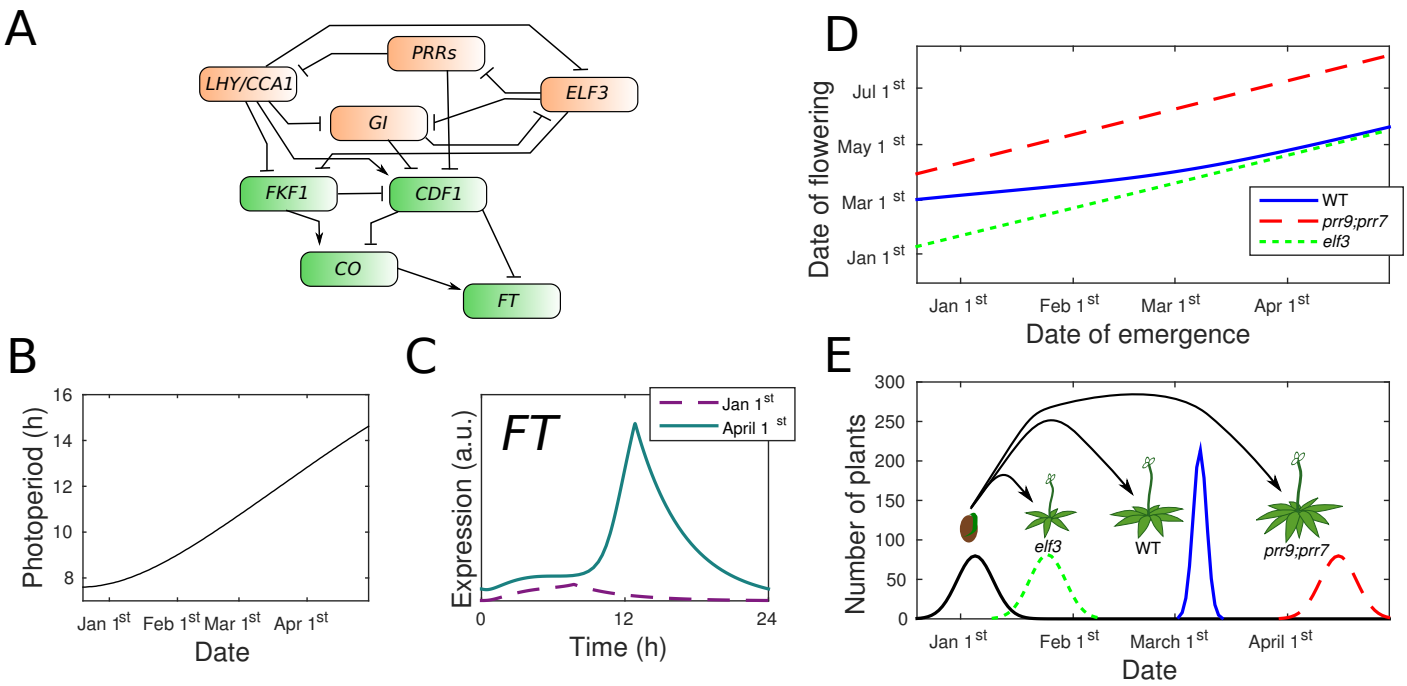

Box 1. Connecting molecular circuits to flowering phenotypes. The regulatory mechanisms underlying the sensitivity of flowering time to photoperiod have been characterised at a molecular level. This is illustrated in (A), showing a simplified representation of the regulatory interactions involved in the circadian clock (orange) and the photoperiod pathway (green), culminating in the regulation of *FT*. The dynamics of these networks have previously been described by mathematical models (Salazar *et al.*, 2009; Pokhilko *et al.*, 2012; Song *et al.*, 2012), and were recently combined and updated in a single model (Seaton *et al.*, 2015). This allows simulation of the behaviour of this network in different natural photoperiods at different times of year, for example those occurring in Halle, Germany (B). At different times of year, the model simulates different levels of *FT* at this location (C). Thus, given a date of seedling emergence, the date of flowering can be predicted (D). Flowering times for different genotypes can also be predicted, e.g. in the case of the mutants *prr9;prr7* and *elf3* (knock-out mutants of circadian clock genes with orthologs in crop species (Staiger *et al.*, 2013)). This allows simulation of a population of plants that show a distribution of dates of emergence. As shown in (E), the sensitivity of the wild-type plants to photoperiod means that flowering occurs over a narrower distribution of dates than either the late-flowering (*prr9;prr7*) or early-flowering (*elf3*) circadian clock mutants.